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Sleep-related memory consolidation in the psychosis spectrum phenotype

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ABSTRACT

Sleep and memory processing impairments range from mild to severe in the psychosis spectrum. Relationships between memory processing and sleep characteristics have been described for schizophrenia, including unaffected first-degree relatives, but they are less clear across other high-risk groups within the psychosis spectrum. In this study, we investigated high-risk individuals with accumulated risk-factors for psychosis and subthreshold symptoms. Out of 1898 screened individuals, 44 age- and sex-matched participants were sub-grouped into those with substantial environmental risk factors for psychosis and subthreshold psychotic symptoms (high-risk group) and those without these phenotypes (low-risk controls). Four groups (high/low risk, morning/evening training) were trained and tested in the laboratory for sustained attention, motor skill memory (finger-tapping task) and declarative memory (word-pair learning task) immediately after training, again after a night of EEG-recorded sleep at home *or* a period of daytime wakefulness, and again after 24 h from training. No differences in sustained attention or in memory consolidation of declarative and motor skill memory were found between groups for any time period tested. However, a group difference was found for rapid-eye movement (REM) sleep in relation to motor skill memory: the longer the total sleep time, particularly longer REM sleep, the greater the performance gain, which occurred only in high-risk individuals. In conclusion, our results suggest a gain in motor skill performance with sufficient sleep opportunity for longer REM sleep in high-risk individuals with subthreshold psychotic symptoms. Declarative memory did not benefit from sleep consolidation above or beyond that of the control group.

1. Introduction

Cognitive ability is time-of-day dependent and intrinsically tied to sleep and wakefulness. It is well established that sleep can stabilise, as well as enhance, performance on both declarative and motor skill learning tasks (Stickgold, 2005; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002; Wilson, Baran, Pace-Schott, Ivry, & Spencer, 2012). The respective roles for non-rapid eye movement (NREM) and REM sleep in these different processes are difficult to tease apart. It is hypothesised that a spatio-temporal coordination between cortico-thalamic slow waves, sleep spindles and hippocampal sharp-wave ripples is needed during NREM sleep (Manoach, Mylonas, & Baxter, 2020). Theta oscillations and ponto-geniculo-occipital (PGO) waves are then thought to facilitate communication between local networks and across distant cortical areas during REM sleep, possibly through temporal coupling and reorganisation of memory information (Vyazovskiy & Delogu, 2014).

In patients diagnosed with schizophrenia, cognitive impairment is a core feature of the illness and often entangled with abnormal sleep profiles (Berkovitch, Del Cul, Maheu, & Dehaene, 2018; Forest et al., 2007; Liu et al., 2002; O'Carroll, 2000; Orzack, Hartmann, & Kornetsky, 1977; Wulff & Joyce, 2011). Many studies suggest that the expected enhancement in memory performance after sleep is largely absent in patients, which seems to be linked to a reduction in stage 2 NREM sleep and a reduction and incoherence in sleep spindle formation (Ferrarelli et al., 2007; Göder et al., 2015; Manoach et al., 2004, 2014, 2010; Seeck-Hirschner et al., 2010; Tesler et al., 2015; Wamsley et al., 2012). Apart from schizophrenia, sleep-related memory consolidation impairments are also present in patients with insomnia, major depression and posttraumatic stress disorder (reviewed in Goerke, Müller, & Cohrs,

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2017), showing that different profiles of associations exist. Mechanisms underlying specific memory consolidation processes in schizophrenia may not only involve sleep spindle activity (reviewed in Ferrarelli & Tononi, 2017; Manoach et al., 2020; Manoach, Pan, Purcell, & Stickgold, 2016) but also slow-waves (Genzel et al., 2015; Kaskie, Gill, & Ferrarelli, 2019; Manoach & Stickgold, 2009) and REM-sleep (Klinzing, Niethard, & Born, 2019), the latter likely, but unproven, to function as a selection mechanism for which memories are going to remain and which will be removed.

Within the psychosis spectrum phenotype, those identified as *clinically* Ultra-High Risk individuals (Lunsford-Avery, Dean, & Mittal, 2017) have more impairments in cognitive abilities associated with increased self-reported sleep disturbances, whereas those identified as being *genetically* at high risk (first-degree relatives of schizophrenia), have cognitive impairments associated specifically with reduced fast sleep spindle density (in the absence of any sleep disorder) (Schilling et al., 2017). Environmental risk exposures, such as childhood adversities and stressful life events, have pronounced effects on sleep. They can impact through acute and chronic stressors on neurodevelopment and sleep, which can predispose to later development of psychotic experiences (Harrison & Weinberger, 2005; Jeppesen et al., 2015; Matheson, Shepherd, Laurens, & Carr, 2011; van Os, Kenis, & Rutten, 2010).

Despite a growing number of studies crossing syndromal boundaries, there is a knowledge gap on sleep spindle features and their relevance to sleep-related memory functions in individuals presenting the psychosis phenotype with a high load of *environmental* risk exposures (current or past) and subthreshold levels of psychotic symptoms. The aim of this study was to close this gap and document whether sleep-related memory performance in these high-risk individuals would differ from that of control subjects without accumulated risk factors and a psychosis phenotype. We applied a multi-domain approach in selecting individuals with either a low or high load of symptomatic and environmental risk factors (Purple et al., in prep). For the experiment reported in here, we conducted home electroencephalography (EEG) sleep studies and compared the level of sustained attention, motor skill memory (finger-tapping sequence task) and declarative memory (word-pair learning task) over three consecutive time windows, one including day-time wake only, one including a night of sleep, and one over 24 h. We hypothesised that high-risk participants would show attenuated gain in sleep-related memory performance compared to the matched control participants and we speculated this would be related to altered sleep spindle activity considering our sample was selected for the purpose of increased risk for psychosis and current literature reports on a functional relationship between sleep spindle formation and psychosis.

2. Methodology

2.1. Sample

Forty-four participants, aged between 18 and 30 years, were recruited from 1898 individuals of the general population, who completed an online survey documenting psychotic-like experiences, established risk factors for psychosis, various mental health variables, habitual sleep behaviour and chronotype (see supplementary methods). This survey is a longitudinal project over the course of 5 years to which data is annually collected. High-risk participants were selected from the top 15% of individuals in this survey for having a high load of environmental risk factors, sub-clinical psychotic symptoms and 3/4 reporting a positive family history of a psychiatric diagnosis, with low-risk participants selected from the bottom 15%. Self-rated state measures of depression, anxiety and stress, and help-seeking behaviour were also selected to identify more clinically relevant individuals (see supplementary methods). Participants were excluded if they had travelled across more than one time zone in the past two weeks; were pregnant; had epilepsy; or had taken any medication for a mental health problem (including sleep problems) within the last 3 months. In addition, low-risk participants were excluded, if they had a history of any mental health disorders and high-risk participants were excluded, if they had a history of a diagnosed psychotic disorder or psychotic episode. All participants provided written informed consent and received an honorarium for their time. The study was conducted in accordance with the Declaration of Helsinki and approved by the North-West Liverpool Central NHS Research Ethics Committee (REC: 14/NW/1142).

2.2. Measures and procedures

2.2.1. Experimental design

During the 3-day protocol, participants completed interviews on their mental state, underwent two nights of at-home polysomnography (PSG), and were tested on a measure of sustained attention and two measures of sleep-related memory: the Finger-tapping Motor Sequence Task (MST) and the Word-Pair Learning Task (WPLT). For both sleep-related memory tasks, participants were randomised into a morning group and an evening group, counterbalanced for high-risk and low-risk groupings. The morning group completed the tasks on day 2 of the study at ~ 9am, 9 pm and day 3 at 9am. The evening group completed the tasks on day 2 of the study at ~ 9 pm, and on day 3 at ~ 9am and ~ 9 pm. Times were adjusted to fit participant's normal routines but were always maintained with a 12 ± 1 h difference between sessions. The MST and WPLT were given in a randomised order between participants but kept in the same order across trials for each participant (Fig. 1).

2.2.2. Questionnaires

Clinical psychosis risk state, chronotype, subjective sleep quality and alertness was assessed with the 'Comprehensive Assessment of At-Risk Mental State' (CAARMS), 'Munich Chronotype Questionnaire' (MCTQ), 'Pittsburgh Sleep Quality Index' (PSQI) and 'Stanford Sleepiness Scale' (SSS) respectively (see supplementary methods).

2.2.3. Polysomnography (PSG)

At-home PSG was recorded with the SomnoScreen + PSG from SOMNOmedics GmbH using a standard bilateral montage of 11 channels (Fp1, Fp2, F3, F4, C3, Cz, C4, P3, P4, O1, O2) referenced to the mastoids. Signals were sampled at 128 Hz and digitally filtered using finite impulse response (FIR) band pass filtering between 0.2 Hz and 35 Hz with a Hamming window function applied. All PSG was set up in the laboratory and data collected in the participant's home environment where they were encouraged to follow their usual daily routines. The first night was used as an adaptation night, and the data were analysed from the second night's recording (Agnew, Webb, & Williams, 1966). PSG data were analysed using the DOMINO version 2.6.0 software (SOMNOmedics GMbH) and scored at 30 s epochs according to the American Academy of Sleep Medicine with the separation of stage 3 and 4 to gain greater macrostructural detail (Iber, Ancoli-Israel, Chesson, & Quan, 2007). Sleep spindles (11–16 Hz) were analysed from central C4 channel using an automatic detection algorithm based upon previous methodologies (Ferrarelli et al., 2007) and limited to artefact free NREM sleep stages 2–4 (see supplementary methods).

2.2.4. Non-declarative motor skill memory

The finger-tapping motor sequence task (MST) is a classical measure of non-declarative motor skill memory (Walker et al., 2002). In this task participants are asked to type a five element sequence (4–1-3–2-4) "as quickly and accurately as possible" for a period of 30 s for a total of 12 trials with a 30 s break period between each trial. During the task, the numeric sequence was displayed on a computer screen in white against a green background to minimise working memory requirements. A white asterisk was used to underline which key should be pressed next

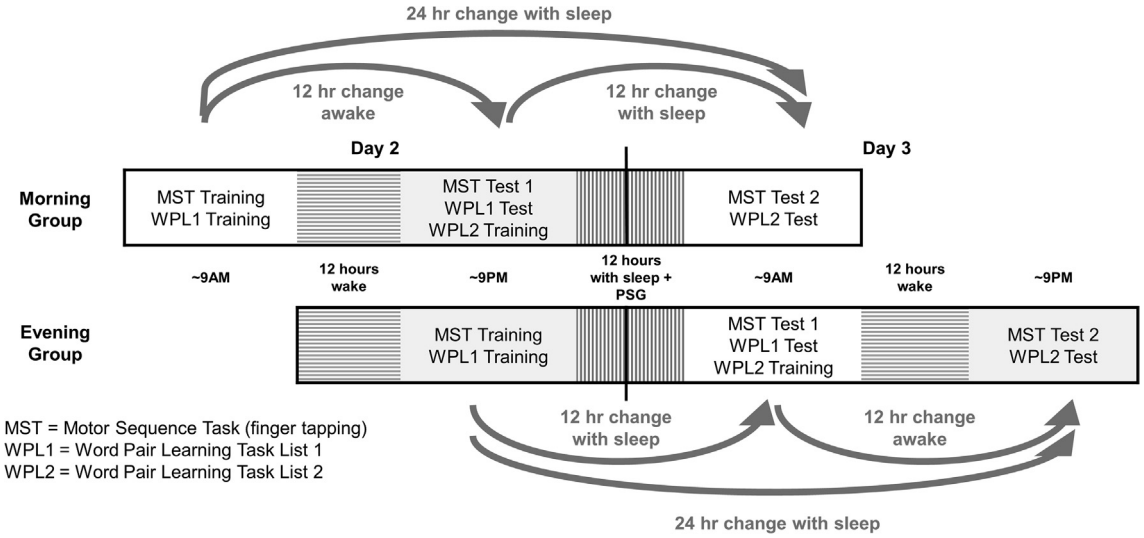

Fig. 1. Experimental design. Two groups, a morning group and an evening group, subdivided into psychosis risk, underwent training and testing for the two following measures of sleep-related memory: In the Motor-Sequence Task (MST, finger-tapping) participants repeated a 5-digit numerical sequence on a keyboard for 30 s per trial for a total of 10 trials. This was then immediately tested for a further two trials and again 12 and 24 h later. In the Word-Pair Learning Task (WPLT), participants learned one of two lists of word pairs (WPL1 = Word-pair list 1, WPL2 = Word-pair list 2) and were then immediately tested through recall of the second word from the pair when presented with the first word. This was repeated after 12 h. After this, participants then learnt the second word-pair list, were immediately tested and then retested after a further 12 h. The order of the MST and the two WPLT was randomized across participants. Overnight polysomnography (PSG) was recorded during the participant's sleep period at home. Arrows indicate the test of interest from those timings. Horizontal stripes indicate awake period, vertical stripes indicate sleep period.

(and moved as the sequence progressed). During the 30 s interlude between trials, a red screen was displayed with the word "Break". Approximately 12 and 24 h after the initial learning session the same task was re-tested for a further 2 trials each. Each 30 s trial was scored for the number of correct sequences and errors. One participant was excluded from this analysis for incorrectly completing the task.

2.2.5. Declarative memory

A Word-Pair Learning Task (WPLT) was used as a measure of declarative memory as used previously (Donohue & Spencer, 2011; Wilson et al., 2012). 64 high-frequency monosyllable concrete nouns were selected and paired to create 32 semantically unrelated word pairs (e.g. Ice-Dog). The task involved 4 stages. During encoding, participants were presented with each of the 32 word pairs successively, each lasting 4 s (inter-stimulus interval of 250 ms), with one word centred on each half of the computer screen. Participants were instructed to pay close attention to each word pair since they were to be tested on them later. Specifically, participants were instructed "To remember the pairs, it is helpful to think of associations between the pairs. For example, if the words were frame-shoe, you might imagine a framed painting of a shoe". Immediately after, participants began an 'immediate recall phase'. During this phase participants were randomly presented with the first word of each word pair only and asked to call out the corresponding word. The researcher then typed this on the screen. Feedback was provided as "correct" or "wrong" followed by the correct pairing, displayed for 750 ms if wrong. Participants were encouraged to guess if they did not know. Participants repeated this for 30 of the word-pairs (excluding the first and last for primacy and recency effects (Plihal & Born, 1997)) until at least 62% accuracy had been reached or until the word-pair list had cycled 5 times. The order of word presentation was randomized across each cycle. A delayed recall phase then followed with the words presented a final time, without any feedback. Approximately 12 h later, the delayed recall was repeated once more. Participants were then told a new list with new word pairs would be given. The protocol was repeated to allow both a sleep and wake condition. Since performance in the immediate recall phase was very high for the first ten participants (average 84% recall accuracy compared to 74% in a previous study (Wilson et al., 2012)), for the remaining participants the word-pair lists were increased to 40 to prevent potential ceiling effects, nonetheless average recall accuracy remained high. Since the delayed recall output expresses recall accuracy as a percentage of original immediate recall accuracy, all participants were included in statistical analysis. Taking the initial ten participants out of the statistical analysis made no difference to the pattern of results.

2.2.6. Attention task

To control for a possible confounding influence of sustained attention, the CANTAB (Cambridge Cognition Ltd, Cambridge, UK) Rapid Visual Information Processing (RVP) test was administered. This 10-minute test requires participants to watch a sequence of pseudo-random digits from 2 to 9 appearing one at a time within a white box in the centre of the screen. Participants are asked to detect a target sequence of digits (e.g. 3–5-7) and respond as quickly as possible, by clicking a button, upon seeing the final digit of the target sequence. The RVP produces nine outcome measures covering latency, probabilities and sensitivity. All participants completed the RVP on the second evening of the study, after set-up of the polysomnography.

2.3. Statistical analysis

For the MST the primary outcome measure was the performance in accuracy measured as average number of sequences typed within a 30 s trial (average of last 2 trials out of a total of 12 trials during training [baseline] and average of the 2 trials after 12 h [Test 1], and average of the 2 trials after 24 h [Test 2]). A sleep effect was identified if participants significantly improved after a period of sleep but not with the equivalent period of wake. For the WPLT the primary outcome measure was the percentage change in number of words recalled from immediate recall (baseline) to delayed recall (12 h later). Since participants tend to show a decrease in the number of words recalled after a delay, the WPLT can measure the effect of sleep in attenuating the amount of forgetting (Wilson et al., 2012). All statistical analyses were computed using 'R' software version 3.3.3 (R Core Team, 2017). Group differences were calculated using ANOVA, post-hoc t-tests for normal

data, non-parametric Wilcoxon rank sum tests for non-normal data, and Chi-squared tests for count data. For the MST, a repeated measures analysis of variance (RM-ANOVA) was used to compare performance across the three time points within each of the four groups. In a between-group design, the post-sleep retest of the high-risk group was compared against the low-risk group. Pearson's product moment correlation coefficients were used to explore the relationship between the memory tasks and sleep parameters. False discovery rate due to multiple comparisons was controlled by applying the Bonferroni family-wise error rate correction method from the package 'R'. All data were reported as mean ± standard error unless otherwise stated.

3. Results

3.1. Participants

Forty-four individuals (22 high-risk, 22 low-risk) completed the study. The groups did not differ in age, gender, menstrual cycle day (in females) or proportion of students compared to non-students, but the psychosis high-risk individuals reported a greater accumulation of risk factors, more subthreshold symptoms of psychosis, negative affect, anxiety and poorer subjective sleep quality (Table 1).

3.2. Motor skill memory - MST performance

For the MST the average number of sequences at baseline was 20.07 ± 5.97 in the high-risk group and 19.98 ± 4.88 in the low risk group with no differences between groups (*t*-test: t = 0.06, p = 0.956). All four groups (high vs. low risk, evening vs. morning) presented a significant increase in the number of correct sequences typed after 24 h (from baseline learning to test 2). A significant improvement was found in performance after 12 h with sleep, but not the subsequent 12 h of wake, for high-risk participants who trained in the evening (RM-ANOVA: F(2,18) = 7.256, p = 0.005; Table 2, Fig. 2Ai). High-risk individuals trained in the morning (Fig. 2Bi) showed an improvement after 24 hours but not after 12 h of wake or 12 h with sleep (RM-ANOVA: high risk, F(2,20) = 8.630, p = 0.002, Table 2, Fig. 2Bi). The low-risk participants trained in the evening (Fig. 2Aii) showed an improvement after both, 12 h of wake and 12 h with sleep (RM-ANOVA: low-risk, F(2,20) = 22.782, p < 0.001, Table 2) and the group trained in the morning showed a significant increase in the number of sequences typed correctly after 12 h with sleep, but not after the initial 12 h of wake (RM-ANOVA: F(2,20) = 6.038, p = 0.009; Table 2, Fig. 2Bii). Collapsing morning and evening groups within each risk group revealed no overall group differences between high and low-risk phenotypes in the relative percent improvement of the task after 24 h (*t*-test: t = -0.25, p = 0.804), 12 h with sleep (t = -0.34, p = 0.735) or 12 h of wake (t = -0.03, p = 0.979; Fig. 2C). There were also no overall differences in percent improvement within groups between the sleep and wake conditions (high-risk, t = 0.13, p = 0.897; low-risk, t = 0.40, p = 0.695). A potential influence of chronotype on MST improvement was investigated in two ways and found negative in both approaches: Using mid-sleep point (MSF_{sc}) from self-reported bed times and get-up times showed no relationship with morning group MST improvement after sleep (r = -0.096, p = 0.669) or evening group MST improvement after sleep (r = 0.25, p = 0.283). Two RM-ANOVAs, conducted separately for either being trained in the morning or in the evening, included participants' 'mid-sleep point' as covariate and 'risk group' as factor. No main effects of chronotype or risk group was detected (Morning training: MSF_{sc}, F(1,19) = 0.617, p = 0.442; Risk group, F(1,19) = 0.524, p = 0.478; Evening training: MSF_{sc}, F(1,18) = 1.538, p = 0.231; Risk group, F(1,18) = 0.190, p = 0.668,). The main effects of 'time' remained significant (Morning training: time, F(2,42) = 14.836, p < 0.001; Evening training, time, F(2,40) = 26.071, p < 0.001).

Table 2
Within-subgroup changes in motor skill memory performance over time, tested after a night of sleep, a day of wakefulness and after 24 h from training. + significant change, - non-significant change.

Group	First trained	MST Performance over…			Effect Size
		Night of sleep	Wake period	24-hours	partial eta^2
High-risk	*Evening*	+	–	+	0.521
High-risk	*Morning*	–	–	+	0.761
Low-risk	*Evening*	+	+	+	0.811
Low-risk	*Morning*	+	–	+	0.475

3.3. Declarative memory – WPLT performance

For the WPLT, the average immediate recall accuracy (immediately after training) was 81 ± 13% in the high-risk group and 88 ± 8% in the low-risk group across both word-pair lists. There were no differences in immediate recall accuracy between the two word-pair lists (Wilcox test: W = 835, p = 0.267). Compared to the low-risk group there was a trend towards lower accuracy in the high-risk group (average of both lists, Wilcox test: W = 157, p = 0.05). No differences were identified in the percentage of words recalled correctly between high and low risk individuals when re-tested 12 h later across sleep (average % change in words recalled, high-risk: −5.53 ± 4.86%, low-

Table 1
Demographics, self-rated mental state and subjective sleep quality between high and low risk groups. Eleven females (high-risk, n = 6, low-risk, n = 5) reported having no period due to taking contraceptives and their menstrual cycle day could not be calculated. Data show means ± standard deviation or % [count] where relevant. * = *t*-test, ^ = chi-squared test, " = Wilcoxon rank sum test. PSQI = Pittsburgh Sleep Quality Index, PQ-16 = Prodromal questionnaire with 16 items, DASS-21 = Depression, Anxiety, Stress Scale with 21 items, FH+, 1st degree = Family History positive at first degree relative sharing 50% of their genes (parents, offspring, siblings).

Demographics and mental state	High-risk, n = 22	Low-risk, n = 22	Test value	p
Mean age	22 ± 3	22 ± 3	0.37*	0.715
Female	73% [16]	68% [15]	0^	1
Menstrual cycle day (females)	12.3 ± 9.04	11.5 ± 8.15	−0.208*	0.828
Student	73% [16]	95% [21]	2.72^	0.099
Risk factors for psychosis	6.8 ± 1.5	2.1 ± 0.9	12.42*	< 0.001
Subjective sleep quality (PSQI)	7.00 ± 2.16	3.40 ± 1.97	428.5"	< 0.001
Subclinical psychotic symptoms (PQ-16 score > 5)	100% [22]	0% [0]	40.09^	< 0.001
Depression (DASS-21 > 13)	82% [18]	5% [1]	24.71^	< 0.001
Anxiety (DASS-21 > 9)	77% [17]	0% [0]	24.54^	< 0.001
Stress (DASS-21 > 18)	82% [18]	0% [0]	27.17^	< 0.001
Help-seeking (yes)	64% [14]	0% [0]	17.71^	< 0.001
FH+, 1st degree any diagnosis	50% [11]	5% [1]	9.28^	0.002
FH+, 1st degree psychosis	5% [1]	0% [0]	0^	1

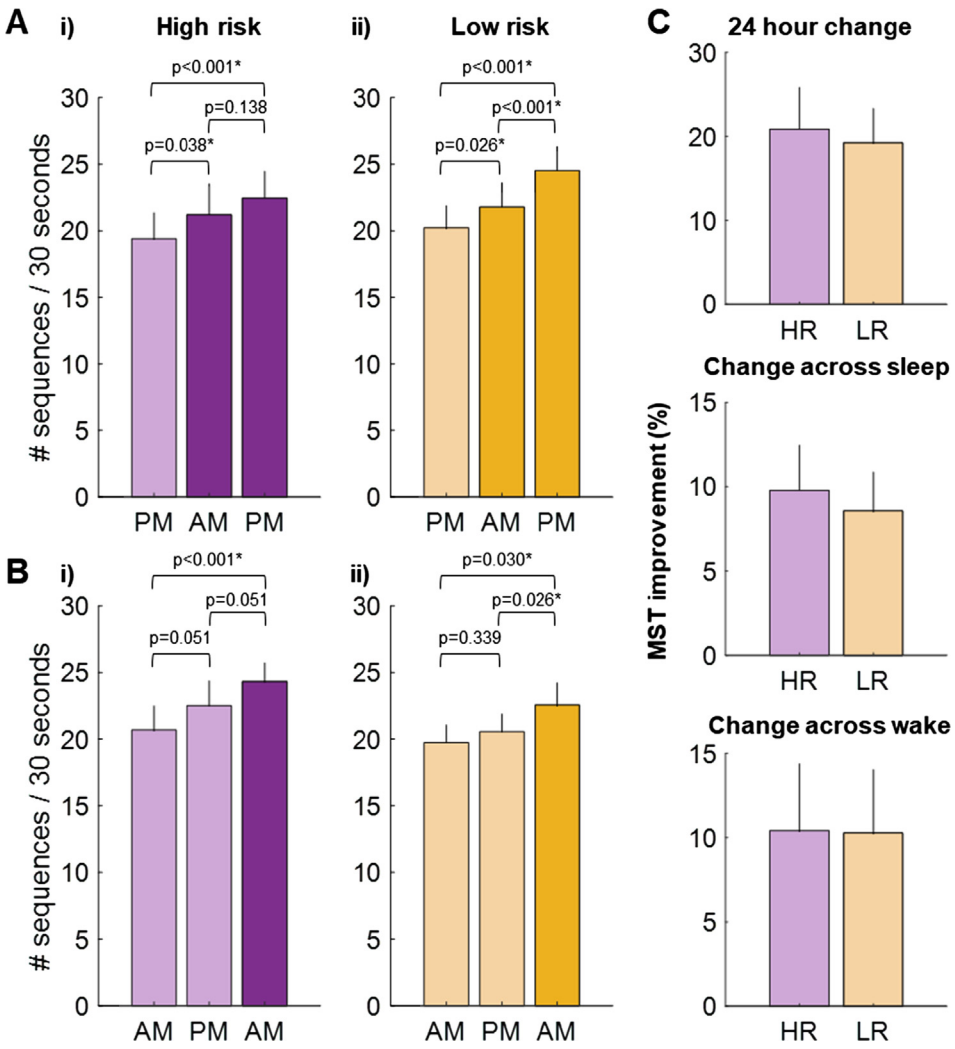

Fig. 2. Effects of sleep and wake on motor skill memory. (A) Half of participants, subdivided into high-risk (purple) and low-risk (yellow), began training of the motor sequence task (MST) in the evening (PM; i: high-risk, n = 10; ii: low-risk, n = 11), were tested 12 h later across sleep (AM) and retested a further 12 h later across wake (PM). (B) The remaining half of the participants began training in the morning (AM; i: high-risk, n = 11; ii: low-risk, n = 11), were tested 12 h later across wake (PM) and retested a further 12 h later across sleep (AM). Darkened bars indicate tests after sleep. P-values refer to the repeated measures analysis of variance within-group post-hoc tests. (C) No differences were identified in the percentage of improvement on the MST between high and low-risk individuals after 24 h, 12 h with sleep or 12 h with wake (two-sample *t*-test, p > 0.05; high-risk n = 21, low-risk, n = 22). Bars denote Standard error. HR = high-risk, LR = low-risk.

risk: −5.27 ± 5.55%; two sample *t*-test, t = 0.17, p = 0.867) or wake (average % change in words recalled, high-risk: −5.04 ± 5.85%, low-risk: −4.81 ± 8.61%; t = 0.10, p = 0.919). Furthermore, no differences were identified within groups between sleep and wake conditions (high-risk sleep vs wake: t = -0.30, p = 0.767; low-risk sleep vs wake: t = -0.21, p = 0.836).

3.4. Task order effects

The task order between the MST and WPLT tasks had no effect on the performance of these tasks (performance for: MST change with sleep, t = 0.08, p = 0.93; MST change with wake, t = -1.67, p = 0.10; WPLT change with sleep, t = -1.66, p = 0.10; WPLT change with wake, t = 1.37, p = 0.18).

3.5. Sleep architecture and task performance

High and low risk group data across one night of sleep did not differ in EEG sleep characteristics, including total sleep time, time spent in each sleep stage, or sleep spindle number and density as reported in Table S2 under supplementary material. High-risk individuals showed a positive correlation between total sleep time and overnight improvement in motor skill performance that was not significant after correcting for multiple testing (r = 0.48, p = 0.147; Fig. 3A). An analysis of individual sleep stages revealed this correlation to be specifically driven by the total amount of REM sleep, whose correlation remained significant after correcting for multiple testing (r = 0.56, p = 0.042). It tended to be maintained when comparing the amount of REM sleep as a percentage of the total sleep time (r = 0.54, p = 0.060). No significant correlations were identified for the amount of stage 1, stage 2 or stage 3 (Fig. 3B). Low-risk individuals showed no significant correlations between any sleep parameter and motor skill performance. Motor skill performance was not correlated with either the number of spindles or spindle density for either group (spindle number: High-risk, r = 0.36, p = 0.105, Low-risk, r = 0.10, p = 0.656; spindle density: High-risk, r = 0.08, p = 0.741, Low-risk, r = 0.01, p = 0.972).

For the declarative WPLT, the percentage of words recalled across sleep was not correlated to EEG total sleep time, the amount of time in each stage of sleep or sleep spindle characteristics for either high or low-risk groups (Supplementary Table S3).

3.6. Subjective alertness and sustained attention

High-risk individuals, in comparison to low-risk individuals, reported significantly lower perceived alertness levels prior to the first tests, regardless of whether the tests were in the morning or evening. Differences in perceived alertness between the groups were not reported at any other time, neither before training sessions nor prior to the second test phase (Table 3). There were no differences on any measure of the rapid visual information processing (RVP) task, including the total number of correctly detected target sequences or the mean latency in detecting these sequences, suggesting no attentional differences between groups (Table 3).

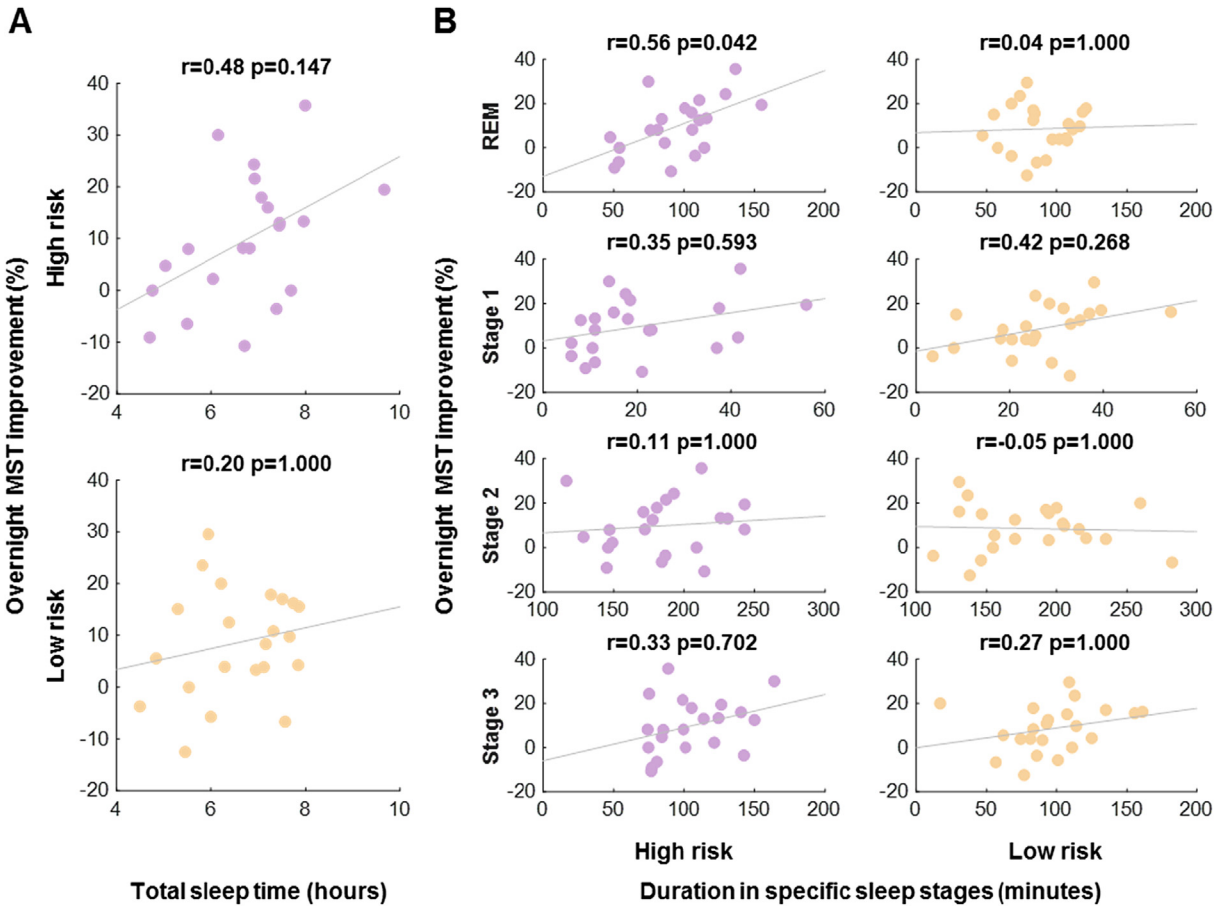

Fig. 3. Correlation between total sleep time (A) and total time in each sleep stage (B) with the percent of overnight improvement in the motor sequence task (MST). Note the significant correlation in high-risk individuals between overnight MST improvement and total amount of REM sleep, which remains after adjusting for multiple comparisons. High-risk, n = 21; Low-risk, n = 22.

Table 3
Group differences in subjective alertness and sustained attention. Subjective alertness was compared between high and low risk groups prior to training, the first test period and the second test period separated based on whether these were in the morning (AM) or evening (PM). Sustained attention was measured using the rapid visual information processing (RVP) task based on the total number of correctly detected target sequences and the mean latency in detecting these sequences. Data show mean ± standard deviation, two-sample *t*-test.

Test	High-risk	Low-risk	t	p
Subjective alertness				
Training AM	2.64 ± 0.81	2.27 ± 0.79	1.07	0.298
Training PM	2.91 ± 1.14	3.00 ± 1.10	−0.19	0.85
Test 1 AM	2.55 ± 0.52	1.73 ± 0.79	2.87	0.01
Test 1 PM	3.91 ± 1.04	2.55 ± 1.04	3.07	0.006
Test 2 AM	2.45 ± 0.93	2.09 ± 0.70	1.03	0.315
Test 2 PM	2.55 ± 1.13	2.09 ± 0.83	1.08	0.296
RVP task				
Number correct	18.73 ± 6.23	21.23 ± 4.36	−1.54	0.13
Mean latency	383.53 ± 65.23	370.94 ± 49.31	0.72	0.47

4. Discussion

In the present study, we tested sleep-related performance in declarative and motor skill memory in individuals with a psychosis spectrum phenotype, who reported a high load of environmental risk exposure, subthreshold levels of psychotic symptoms, anxiety, depressive mood and poor sleep quality and the results were compared with those of healthy controls without such factors and symptoms. Our first hypothesis that psychosis risk individuals would show attenuated gain in sleep-dependent memory performance was not supported by our results, which tested against a wake control condition. With regard to motor skills, performance improved significantly over a period of 24 h in both groups with no difference in the percentage of improvements on the motor skill task across any time window tested, i.e. 12 h wake, 12 h overnight and 24 h. It is noteworthy that in 3 out of 4 groups, significant performance gain occurred *within* subjects after a period of sleep, while after a period of wake, it occurred in 1 out of 4 groups, irrespective of being trained in the morning or evening.

Previous published studies not including a wake control condition, reported a performance gain in motor skills with sleep in medicated patients diagnosed with schizophrenia when compared against healthy individuals (Genzel, Ali, Dresler, Steiger, & Tesfaye, 2011; Manoach et al., 2004; Wamsley et al., 2012). Manoach et al. (2010) included a wake control condition and identified no gain across either sleep or wake intervals in the patients, whereas a significant gain in performance occurred under both conditions in healthy controls, suggesting no specific effects from sleep but a lack due to the underlying disorder (Manoach et al., 2010). Comparing our results with findings of Manoach et al. (2010), our high-risk group appears as competent in learning and retrieving motor memory skills across both conditions as Manoach's control group. Consequently, as far as memory performance is concerned, our high-risk phenotype does not represent an intermediate group along the spectrum from healthy to severely ill individuals. With 73 percent being students and a sleep efficiency of 90 percent (objectively measured) this group appears to be well educated and high functioning, which may confer a protective impact in the presence of risk factors (i.e. positive family history, subthreshold

psychotic and affective symptoms).

The declarative memory performance of the high-risk individuals resembled that of healthy controls with both groups showing only a minimal degree of change in performance from training to testing for any time period investigated. This points towards the learning task not having been difficult enough, which could have led to ceiling effects, a possibility that has previously been shown to determine whether a sleep effect is detectable or not in schizophrenia (Göder et al., 2015; Seeck-Hirschner et al., 2010).

Our second hypothesis of a relationship between overnight memory performance and sleep spindle activity in the high-risk group was also not supported by the sleep data. The unimpaired cognitive performance and the intact EEG sleep characteristics in the present study groups converge with EEG findings of similar sleep consolidation studies where controls and patients with psychotic disorders other than schizophrenia, showed non-significant correlations (Manoach et al., 2014, 2010; Wamsley et al., 2012). In turn, three studies testing first-degree relatives of patients diagnosed with schizophrenia (D'Agostino et al., 2018; Manoach et al., 2014; Schilling et al., 2017) document various spindle profiles. Therefore, two explanations for the absence of a sleep-related memory consolidation phenotype in our high-risk sample emerge: first, lower genetic load by heritability to a diagnosis other than schizophrenia and absence of negative vulnerability such as cognitive deficits; and second, possible protective factors such as high level of education and objectively adequate sleep duration, despite the individuals' positive symptoms and accumulated risk factors for psychosis.

The relationships of specific sleep parameters to specific cognitive performances in the high-risk group resembled those of the low-risk group, except for REM sleep duration. In our exploratory analysis, longer REM sleep was statistically significantly associated with greater percentage of gain on the motor sequence task in the high-risk group only. A similar observation in another exploratory analysis (Fischer, Hallschmid, Elsner, & Born, 2002) also indicated greater gains in motor skill performance in healthy volunteers with high amounts of REM sleep. We speculate that our finding being specific to the high-risk group, could be related to their greater variance in REM sleep duration, which might expose its benefits on memory performance. This idea coincides with our observations of the concomitance of biological and psychological factors of sleep, in which a quantitative lack of sleep, in combination with self-perceived poor sleep quality, increases the vulnerability to endorse psychotic-like symptoms, while adequate amounts of sleep protect from this cognitive vulnerability (Cosgrave et al., 2018).

Contrariwise, in a well-controlled experiment using acute pharmacological REM sleep blockade on the consolidation of finger sequence tapping accuracy in healthy individuals, Rasch et al showed that REM sleep is not required for the consolidation of motor skill memories (Rasch, Pommer, Diekelmann, & Born, 2009). Given these inconsistencies, the group difference in our study might be due to unrecognised third factors or a spurious finding as the sample size was modest and the variability for both parameters were larger in the high-risk group. About 69% of the variation in MST improvement is anticipated to reflect reasons not connected to the relationship with REM sleep. Therefore, it remains to be seen whether there is a role for REM sleep in high-risk individuals beyond a correlation.

The use of a sample of high-risk participants selected not exclusively by clinical symptoms of psychosis but by an accumulation of risk factors for psychosis to investigate sleep-related memory consolidation may be perceived as a limitation in not being sufficient to reveal all psychosis-relevant memory consolidation characteristics. However, the chosen groups serve along the continuum as an 'extended' environmental risk grouping and 'outer group' comparator for findings from clinical ultra-high risk and genetically predisposed samples, which is important for the refinement of environmental risk management for the prevention of psychosis. In this regard, two participants from the high-risk group reported a diagnosis of a new psychiatric, but non-psychotic, disorder after a year's follow-up.

A mix of objective and self-reported measures were employed in the study, of which the self-reported measures are known to be prone to response bias, for example due to the participant's social desires. Nevertheless, the strength of complementary subjective data lies in understanding as much as possible of a participant's mental state suggesting that there is a true advantage in combining experimental paradigms with self-assessed perceptions of health, not least to collect information on the variability and the level of discrepancy between objective and subjective response. Finally, the sample size was modest and although protocol completion was excellent, power might have been reduced.

In conclusion, this study reports evidence of intact consolidation of memories across waking and sleep in the domains of declarative facts and motor skill learning in young adults with subthreshold psychotic symptoms, who also accumulated substantial environmental risk exposures for expression of psychosis. A greater gain in motor skill performance overnight became apparent in individuals with longer sleep, especially REM sleep, in the high-risk group only, whilst EEG sleep profiles, including sleep spindle density, were similar to healthy age- and sex-matched controls. These observations raise awareness on a societal level, in that sufficient sleep for learning and memory is important in at-risk individuals and we suggest investigating whether this can be guaranteed by introducing the 'Right to sleep'' into society as a refinement of the 'Right to life' in an effort to improve environmental risk management for the prevention of psychosis.

CRediT authorship contribution statement

R.J. Purple: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **J. Cosgrave:** Conceptualization, Methodology. **V. Vyazovskiy:** Software. **R.G. Foster:** Funding acquisition. **K. Porcheret:** Conceptualization, Methodology, Writing - review & editing. **K. Wulff:** Conceptualization, Methodology, Writing - review & editing, Visualization, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nlm.2020.107273.

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